ABBOTT

Corporate Regulatory Affairs

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July 20, 1998

The Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices
[Docket No. 98N-0222]

Dear Sirs or Madams:

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 54,000 people around the world with manufacturing sites in 35 countries.

I. SPECIFIC CONCERNS

Statements in question are bolded with comments immediately following.

Subpart B - Information To Be Disseminated

99.101 Information that may be disseminated.

(a) ...Such information shall:

(5) **Not be derived from clinical research conducted by another manufacturer unless the manufacturer disseminating the information has the permission of such other manufacturer to make the dissemination.**

This paragraph may need additional clarification with respect to FDA's intent and the definition of "another manufacturer." For example, clinical research may be sponsored jointly by multiple companies or groups. In these cases, contracts or agreements between sponsors may specify how the data is to be used by the sponsoring companies. Co-sponsoring companies should be responsible to maintain their own agreements without FDA input.

This paragraph also implies that clinical research that has been published remains proprietary. However, the act of publishing information places it in the public domain. A manufacturer who wishes to pursue use of data that has been published by the original sponsor should not be prohibited from doing so as long as proper credit is given.

99.103 Mandatory statements and information

(a) Any information disseminated under this part shall include:

(1) A prominently displayed statement disclosing:

(i) **...If the information to be disseminated includes both approved and unapproved uses or cleared and uncleared uses, the manufacturer shall modify the statement to identify the unapproved or uncleared new use. The manufacturer shall permanently affix the statement to the front of each reprint or copy of an article from a scientific or medical journal and to the front of each reference publication disseminated under this part:**

Clarification is needed regarding articles that discuss more than one new use. As written, this paragraph uses plural and singular forms and creates confusion regarding FDA's intent.

(3) **A bibliography of other articles (that concern reports of clinical investigations both supporting and not supporting the new use) from a scientific reference publication or scientific or medical journal that have been previously published about the new use of the drug or device covered by the information that is being disseminated, unless the disseminated information already includes such a bibliography; and**

This paragraph is vague regarding what needs to be included in the bibliography and under what circumstances a bibliography that is "already

included" will be considered adequate. Additional clarification of this section should be considered.

Subpart C - Manufacturer's Submissions, Requests, and Applications

99.201 Manufacturer's submission to the agency

(a) ...shall submit to the agency:

(2) **...The information and reports required under this paragraph shall include case studies, retrospective reviews, epidemiological studies, adverse event reports, and any other materials concerning adverse effects or risks reported for or associated with the new use. If the manufacturer has no knowledge of clinical trial information relating to the safety or effectiveness of the new use or reports of clinical experience pertaining to the safety of the new use, the manufacturer shall provide a statement to that effect;**

Search requirements have not been clearly established for literature or postmarketing adverse event reports. Standards regarding literature searches and other submission requirements should be clearly delineated in the regulation.

(d) **The 60-day period shall begin when FDA receives a complete submission, including, where applicable, a certification statement or application for exemption. For purposes of this part, a submission shall be considered to be complete if FDA determines that it is sufficiently complete to permit a substantive review.**

This paragraph should also include a clear timeline indicating when FDA will notify manufacturers that a submission is complete. For example, FDA should communicate to a manufacturer within 15 days of receipt that a package is acceptable and will then proceed for substantive review.

Subpart D - FDA Action on Submissions, Requests, and Applications

99.301 Agency action on a submission

(a) Submissions...

(3) Determine that the information submitted regarding a new use fails to provide data, analyses or other written matter that is objective and balanced. If FDA makes such a determination, the agency:

(i) **Shall provide to the manufacturer notice and an opportunity for a meeting regarding the agency's determination:**

This statement should include a specific time frame for the meeting to occur.

(b) *Protocols/Studies*. Within 60 days after receiving a submission under this part, FDA shall:

(1) **...review the manufacturer's proposed protocols and schedule for completing such studies and determine whether the proposed protocols are adequate and whether the proposed schedule for completing the studies is reasonable...**

(2) **...conduct a preliminary review of the completed study reports to determine whether they are potentially adequate to support the filing of a supplemental application for the new use...**

The expertise to accomplish these tasks resides in the reviewing divisions. Clarification as to which functional groups within FDA will be responsible for these tasks is needed, as well as timelines for such review if it is to be conducted within, or in concert with, the reviewing divisions.

99.303 Extension of time for completing planned studies.

(b) **...Extensions under this paragraph shall not exceed 24 months.**

Clarification is needed regarding application of the 24 month extension maximum. Does this statement apply to 99.303 (b) only, or to each section listed under 99.303?

99.305 Exemptions from the requirement to file a supplemental application

(c) FDA may grant an application for an exemption if FDA determines that:

(1) It would be economically prohibitive for the manufacturer to incur the costs necessary to submit a supplemental application for a new use, which at a minimum requires:

(ii) **That the estimated cost of the studies needed to support the submission of a supplemental application for the new use exceed the estimated total revenue from the drug...**

As an alternative, we suggest rewriting to specify "total revenue from the new use..."

Subpart E - Corrective Actions and Cessation of Dissemination

99.401 Corrective actions and cessation of dissemination of information.

(b) FDA actions based on information disseminated by a manufacturer.

(2) ...FDA shall issue such an order only after it has:

(ii) **Provided to the manufacturer an opportunity for a meeting. FDA shall not provide an opportunity for a meeting if the manufacturer certified that it will submit a supplemental application for the new use within 6 months and the noncompliance involves a failure to submit such supplemental application.**

A specific time frame for the meeting to occur should be included.

II. CLOSING REMARKS

While the Agency is required to finalize this proposal on a fast-track basis, we nevertheless recommend that the Agency, at a future point in time, undertake some additional public discussion on this and related subjects.

There has been a considerable amount of activity in this area including several public meetings, this proposed rule and a recent guidance document titled, "Draft Guidance for Industry: Consumer - Directed Broadcast Advertisements (Docket No. 97D-0302).

With these in mind, the Agency could facilitate a greater understanding of this challenging subject through industry-wide discussions and educational efforts. Such activities could be carried out with the support of DIA, AAPS or other scientifically oriented trade association. The Agency could also discuss this on one of the FDA/FDLI telecasts.

Please feel free to contact me on this subject.

Yours truly,

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